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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,011	12/04/2001	Renato V. Iozzo	IOZ01-NP009	7689

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	**PAPER NUMBER**
1642	10

DATE MAILED: 05/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,011	IOZZO, RENATO V.	
	Examin r	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *1-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed 2/25/2003 (paper no. 9) is acknowledged and entered into the record. Accordingly, no claims are canceled and one new claim is added.

2. Claims 1-16 are pending, claims 1-14 are withdrawn from further consideration as being drawn to non-elected inventions. Applicant is reminded to cancel all claims non-elected.

3. Claims 15 and 16 are examined on the record.

Claim Rejections Maintained - 35 USC § 112, 2nd paragraph

4. The rejection of claim 15 and now newly added claim 16, under 35 USC 112, 2nd paragraph is maintained for the reasons of record. Applicant argues that the terms "fragments," "derivatives," and "analogs" are clearly defined in the specification and that such terms are defined as proteins or peptides that have substantially similar amino acid sequence and biological characteristics (both functional and physical) to endorepellin. Applicant further argues that specific fragments are disclosed in the specification which include fragments termed Δ1 and Δ5. Applicant further argues that the arguments that apply for the term "fragment" also apply to the terms "analog" and "derivatives", wherein sequences that are substantially similar but not identical to the endorepellin protein or chemical modifications to derivatize a protein where well known to the skilled artisan at the time of filing. Applicant's arguments have been carefully considered but are not found persuasive. Although the terms themselves are known by the skilled artisan, one of skill in the art would not know the metes and bounds of the terms used in the claims. Applicant argues that the specification provides disclosures to

the artisan so as to fully understand the metes and bounds of the terms, however, such limitations are not found in the claims and as such, one of skill would not understand which fragments, analogs, or derivatives are being claimed. The specification defines the terms in a broad scope, wherein fragments, analogs or derivatives are any amino acid sequences which are substantially similar to the amino acid of endorepellin. Although the breadth of the terms are understood, the terms are still indefinite, because the skilled artisan does not which fragments, analogs or derivatives are being referred.

Claim Rejections Maintained - 35 USC § 112, 2nd paragraph

5. The rejection of claim 15 and now newly added claim 16 under 35 USC 112, 2nd paragraph is maintained for the reasons of record. Applicant argues that endorepellin was fully disclosed in the specification as being a protein of 210-705 amino acids in length because fragments ranging in sizes of 254 and 494 amino acids retained the functional characteristics of endorepellin. Applicant further argues that Murdoch *et al* fully disclosed the sequence of endorepellin, (referred to as domain V of perlecan by Murdoch *et al*) and that one of skill would know at the time of filing the sequence of endorepellin. Applicant's arguments have been carefully considered but are not found persuasive. The specification on page 2 defines the term "endorepellin" as the carboxy terminus of perlecan or domain V of perlecan. Murdoch *et al* discloses domain V as being 705 amino acids in length. Furthermore, Mongiat *et al* (disclosed by the applicant in paper filed 2/25/2003 (paper no. 9)) defines endorepellin as the protein consisting of the entire domain V of perlecan (amino acids 3687-4391) (see page 4240). Further still, the specification then defines "endorepellin" as being between 210 and 705 amino acids

in length (see page 12). One of skill in the art would have a difficult time deciphering the true amino acids sequence represented by the term "endorepellin". As such the term as defined by the specification and further supported by Murdoch *et al* and Mongiat *et al* is indefinite because one of skill in the art would find it difficult to distinguish the true meaning of the term "endorepellin". One of skill would have to determine whether endorepellin is a 210 amino acid protein, a 704 amino acid protein, or a protein that falls within the ranges of 210-705 amino acids.

In addition, endorepellin is a fragment of a larger protein, the desired protein being claimed is a fragment of a larger fragment of perlecan. It is also noted for the record that the instantly claimed protein has not been defined by a sequence. As such the claimed protein is not defined and is considered an indefinite laboratory term.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

6. The rejection of claim 15 and now newly added claim 16, under 35 USC 112, 1st paragraph as lacking proper written description is maintained for the reasons of record. Although it was initially argued that the written description requirement was meet for an endorepellin protein that was between 210-705 amino acid in length and not specifically for any and all fragments, analogs, or derivatives of endorepellin, it is now newly argued, upon further reconsideration, that the written description in this case has only set forth endorepellin proteins that are of 704 (full length), 494 (Δ1), 239 (Δ 2), 106 (Δ 3), 78 (Δ 4), 254 (Δ 5), 283 (Δ 6), and 209 (Δ 7) amino acids in length and therefore the written description is not commensurate in scope to any and all endorepellin fragments, analogs, and derivatives. Applicant argues that the specification has provided clear

indication that the invention was in their possession at the time of filing and that the invention not need be disclosed *ipsis verbis*, but rather provide the skilled artisan with enough guidance so as to practice or make the invention and to demonstrate that the applcaint was in possession of the claimed invention. Applicant's arguments have been carefully considered but are not found persuasive. First, it is noted that the instant specification is missing sequence identification numbers that specifically identify the fragments claimed with an associated sequence. As such one of ordinary skill in the art would not be able to adequately determine if the sequences claimed are any different from those already disclosed in the prior art. It is also noted that the applicant states on the record that the sequences for the instant protein, endorepellin, are already disclosed in the prior art and that one of skill would be able to determine what the fragments, analogs, or derivatives are encompassed within the scope of the claims. Because the application on it own must be able to disclose to one of skill in the art at the time of filing that the applicant was in possession of the invention, and despite the fact that the sequences were already disclosed in the prior art, the instant specification has not demonstrated to one of skill in the art that the applicant was indeed in possession of any and all fragment, analogs, or derivatives of endorepellin. Furthermore, the instant specification is devoid of any mention or disclosure concerning analogs or derivatives. One of skill in the art would not know the structure or composition of the analogs or derivatives because the specification has not provided the skilled artisan with a SEQ ID No: from which to base the construction of said analogs or derivatives. As such the fragments, analogs, or, derivatives have not meet the requirements for written

description. Therefore, only endorepellin and the fragments named D1-D7 meet the requirements for written description.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

7. The rejection of claims 15 and now newly added claim 16 under 35 USC 112, 1st paragraph as lacking proper enablement is maintained for the reasons of record and for newly argued reasons. Applicant argues that the instant specification clearly discloses how to make the instant invention and further argues that methods of use are clearly outlined in the specification. Applicant points to methods of in vitro assays such as cell migration assays and tube formation assays, and to methods of in vivo activity in such assays as the CAM assay. The applicant then further argues that the references sited are not applicable to the instant invention because the references do not refer to angiogenesis inhibition assays. In addition, the applicant argues that the skilled artisan at the time of filing knew that positive results from in vitro assays were indicative of in vivo success. Applicant arguments have been carefully considered but are not found persuasive. At the time of the invention, several references teach that proteins that have found relative anti-angiogeneic success in vitro have had little effect in human trials. Auerbach *et al* (Clinical Chemistry 2003 49(1):32-40) states that the interpretation of in vitro success of angiogenic assays, at best, provides an initial assessment of compounds for their ability to function effectively in vivo. Auerbach *et al* further states that in vivo analysis is critical for the full interpretation of a compounds effectiveness. Although it is noted that the instant invention provides a semi-in vivo (technically considered an in vitro assay, see Auerbach *et al* pg 36) analysis of

endorepellin in the CAM assay, others have shown that the ability of angiogenic proteins that have potent anit-angiogenic effects in vitro have failed to provide the same type of response in vivo. For example, the in vitro success of two anti-angiogenic proteins, endostatin and angiostatin, has lead investigators to test these proteins in vivo models with relatively little effect in vivo (see Weiss R Washington Post 1998 May 6, A3). Therefore, although the instant specification has provided some evidence for in vitro success, the claims as interpreted have not been enabled for in vivo usage.

NEW ARGUMENTS

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 15 and 16 rejected under 35 U.S.C. 102(b) as being anticipated by Murdoch *et al* (J. Biol. Chem. 1992;267(12):8544-8557). Claims are drawn to a pharmaceutical composition comprising enodrepellin, also known as domain V of perlecan, wherein the endorepellin protein is between 210-705 amino acids in length. Murdoch *et al* discloses a protein that comprises domain V of perlecan, and also specifically discloses of a protein that is 704 amino acids in length (see page 8550).

Claim Rejections - 35 USC § 102

10. Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Snow AD (US Patent 5,958,883). Claims 15 and 16 are drawn to a pharmaceutical

composition comprising endorepellin, wherein the endorepellin protein is between 210 and 705 amino acids in length. Snow AD discloses a perlecan molecule that is administered in vivo (see column 15, for example). Because endorepellin is defined as the carboxy terminus of perlecan or as domain V, and because domain V consists of 704 amino acids, as evidenced by Murdoch *et al* (see above), the claims are anticipated by Snow AD.

Claim Rejections - 35 USC § 102

11. Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Whitelock J *et al* (WO 99/06054). Claims are drawn to a pharmaceutical composition comprising endorepellin, wherein the endorepellin is between 210 and 705 amino acids in length. Whitelock J *et al* disclose a pharmaceutical composition comprising perlecan or active fragments thereof in combination with pharmaceutical carriers and diluents. Because endorepellin is also known as domain V of perlecan and because domain V is 704 amino acids in length (evidenced by Murdoch *et al*), the instantly claimed pharmaceutical composition is anticipated by Whitelock J *et al*.

Conclusion

No claims are allowed. This rejection is made NON-FINAL to allow the applicant a chance to respond to the newly made rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
May 2, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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